REMARKS

Applicants thank the Examiner for review of the instant application. For the reasons stated below, the rejections of the presently pending claims are respectfully traversed. Claims 6-8 and 11-17 are presented for examination.

Status of the Appeal

The Examiner's Answer presented a new ground of rejection. As such, the Examiner's answer properly should have indicated that it included a new ground of rejection, and Applicants should be entitled to request that prosecution be reopened. As provided in M.P.E.P. §1207.03:

> A new prior art reference >applied or< cited for the first time in an examiner's answer generally will constitute a new ground of rejection. If the citation of a new prior art reference is necessary to support a rejection, it must be included in the statement of rejection, which would be considered to introduce a new ground of rejection. **Even if the prior art reference is cited to support the rejection in a minor capacity, it should be positively included in the statement of rejection. In re Hoch, 428 F.2d 1341, 1342 n.3, 166 USPQ 406, 407 n. 3 (CCPA 1970).** **>Where< a newly cited reference is added merely as evidence of the prior ** statement made by the examiner >as to what is "well-known" in the art which was challenged for the first time in the appeal brief<, the citation of the reference in the examiner's answer would not >ordinarily< constitute a new ground of rejection within the meaning of 37 CFR *>41.39(a)(2)<. See also MPEP § 2144.03.**>

The Examiner's answer newly applied and cited Chen *et al.* (Mol. and Cell. Proteomics, (2002) 1:304-313) and Fessler *et al.* (J. Biol. Chem. (2002) 277:31291-31302). These references were cited to support the utility rejection by allegedly standing for the position that there is no strong correlation between protein and transcript levels. Applicants have maintained throughout prosecution that a change in mRNA levels will typically lead to a similar change in the levels of the encoded polypeptpide. Applicants also have maintained throughout their reasons for traversing the PTO's rejections and distinguishing the cited references related to the PTO's assertions that there is no strong correlation between protein and transcript levels. Accordingly, Applicants' Appeal Brief did not challenge for the first time the PTO's position that there is no strong correlation between protein and transcript levels. Therefore, these newly applied references could not have been added as evidence of a prior statement made by the Examiner as to what is "well-known" in the art which was challenged for the first time in the Appeal Brief.

As such, there is no basis for concluding that Examiner's Answer did not present a new ground of rejection.

In view of the above, Applicants herein request acknowledgement that the Examiner's Answer presented a new ground of rejection, and Applicants hereby request that prosecution be reopened.

Status of the Claims

Applicants mailed an Amendment Filed with Notice of Appeal on September 13, 2005, canceling Claims 4 and 5, and amending Claim 12 to change the claim dependency from canceled Claim 4, to Claim 6. The Advisory Action mailed October 12, 2005 states that these amendments have been entered. The listing of the claims above reflects these amendments. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of pending Claims 6-8 and 11-17 under 35 U.S.C. § 101 as lacking utility for the reasons set forth in the previous Office Actions. The PTO states that the specification discloses that the PRO1357 polynucleotide is more highly expressed in normal stomach and lung tissue compared to stomach and lung tumor tissue, respectively. However, the PTO rejects Applicants' asserted utility, explaining that the basis of the utility rejection "is the insufficiency of disclosure to support a specific and substantial or well established utility" because "there is critical information lacking which includes: whether differences in nucleic acid expression of PRO1357 were significant, under what conditions differences could be detected, and what levels (relative or absolute) were detected in tumor and normal control, the skilled artisan cannot use (whether *in vivo* or *in vitro*) the claimed invention." *Office Action* dated June 14, 2005 at page 5.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of

record, the PTO has not met its burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However even if the PTO has met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1357 polypeptide is expressed at least two-fold higher in normal stomach and lung tissues compared to stomach and lung tumor tissue, respectively;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* a decrease, generally leads to a corresponding change in the level of the encoded protein, *e.g.* a decrease;

3. Given Applicants' evidence that the mRNA for the PRO1357 polypeptide is differentially expressed in stomach and lung tumors compared to normal stomach and lung tissue, respectively, it is more likely than not that the PRO1357 polypeptide is also differentially expressed in stomach and lung tumors compared to normal stomach and lung tissue, respectively, making the claimed polypeptides useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making two arguments in response to Applicants' asserted utility:

1. The PTO challenges the reliability of the evidence reported in Example 18, stating for example that there is no guidance in the specification as to how high the expression levels are, and that the literature cautions against drawing conclusions based on small changes in transcript

expression levels between normal and cancerous tissue, citing Hu *et al.* (J. Proteome Res., (2003) 2(4):405-12) for support;

2. The PTO cites Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71), Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30) and Konopka *et al.* (Proc. Natl. Acad. Sci. USA, (1986) 83:4049-52), as supporting the assertion that there is "no strong correlation between protein and transcript levels," and there is a "lack of correlation between gene amplification and increased polypeptide levels." *Office Action* dated June 14, 2005 at pages 5-6. Therefore, further research needs to be done to determine if the increase or decrease in PRO1357 cDNA expression supports a role for the peptide in cancerous tissue. The Examiner's Answer newly cites Chen *et al.* (Mol. and Cell. Proteomics, (2002) 1:304-313) and Fessler *et al.* (J. Biol. Chem. (2002) 277:31291-31302) as supporting this same position.

Applicants respectfully submit that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

The Data in Example 18 are Data Regarding Differential mRNA Levels, not Gene Amplification

Applicants begin by clarifying that the data concerning the differential expression of the PRO1357 gene presented in Example 18 relate to gene expression, **not** gene amplification. The description of Example 18 makes clear that the results were obtained by quantitative PCR amplification of cDNA libraries. It is well known in the art that cDNA libraries are made from mRNA, and reflect the level of mRNA for a particular gene in the source tissue. Thus, Example 18 is reporting a measure of the *expression* of the PRO1357 gene, *i.e.*, mRNA levels, not its *amplification*, *i.e.*, the number of copies of the PRO1357 gene in the genome.

For this reason, the relationship between gene amplification and the level of protein expression is not relevant to the instant application. The distinction between gene amplification and protein expression has been pointed out in previous responses, which are incorporated by reference herein. The PTO maintains citation of Konopka (Proc. Natl. Acad. Sci. USA, (1986) 83:4049-52) as providing "evidence showing lack of correlation of between gene amplification and increased polypeptide levels." *Office Action* dated June 14, 2005, at page 6.

Further, the PTO uses this evidence as basis for the utility rejection:

> Given how small the unknown amount that DNA copy number of PRO1357 decreased in tumors, and the evidence provided by Haynes et al., Hu et al.

> (discussed above) and Konopka et al., one skilled in the art would not have assumed that a small decrease in gene copy number would correlate with significantly increased mRNA or polypeptide levels. The level of decrease of the encoding nucleic acid is not disclosed. One skilled in the art would have to do further research to determine whether or not the PRO1357 polypeptide levels decreased significantly in the tumor samples. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. *Office Action* dated June 14, 2005, at page 6 (emphasis added).

The correlation between gene copy number and mRNA/polypeptide levels is completely irrelevant to the instant application. Applicants have provided reliable evidence of differential PRO1357 mRNA levels in certain tumors by examining cDNA libraries, not genomic DNA. Whether this differential mRNA expression is due to changes in gene copy number, transcription rates, a combination of these, or some other known or unknown cellular mechanism is simply not relevant to Applicants' asserted utility. Regardless of the cause, the differential expression of PRO1357 mRNA and the resulting differential expression of PRO1357 protein can be used as a molecular marker of lung or stomach cancer to assist in the diagnosis of these diseases.

The issues under examination will be greatly simplified if an understanding can be reached that the data in Example 18 reflect the level of mRNA for PRO1357 expressed, *i.e.*, the level of PRO1357 gene expression, and not the number of copies of the PRO1357 gene present in the genome, *i.e.*, gene amplification. Once this is established, it is clear that the gene amplification data of the Konopka reference are not relevant to Applicants' asserted utility, and Applicants' references and declarations regarding the relationship between mRNA levels and protein levels are directly relevant.

The Data Reporting Differential Expression of PRO1357 mRNA are Sufficient to Provide Utility for the mRNA as a Diagnostic Tool

Applicants turn to the PTO's argument that the evidence of differential expression of the gene encoding the PRO1357 polypeptide in normal stomach and lung tissue compared to stomach and lung tumor, respectively, is insufficient, and that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

Applicants note that the PTO has recognized that the teachings in the specification of differential expression of the PRO1357 mRNA are sufficient to establish a utility for SEQ ID NO:77, which encodes the PRO1357 polypeptide: "It is noted that the asserted utility for the nucleic acid of SEQ ID NO:77 or the coding region thereof has been accepted upon further reconsideration." *Office Action* dated June 14, 2005, at page 2. The PTO similarly acknowledged the utility of the PRO1357 polypeptide-encoding nucleotide in the closely related application Serial No. 10/063,711. *See Office Action for Application 10/063,711 dated June 14, 2005* at 2. In that case, the exact same data from Example 18 was relied on for utility of the claimed nucleic acids as diagnostic tools for stomach and lung tumors, and the PTO made the same arguments regarding the insufficiency of the data in Example 18 and the cautionary teachings of Hu *et al.* In response to Applicants' arguments to the contrary, the PTO stated "The rejection of claims [sic] under 35 USC 101 is withdrawn upon further reconsideration." *Id.* at 2. Therefore, Applicants submit that the PTO's rejection of the exact same data in the instant case based on the same arguments of alleged insufficient details or the teaching Hu *et al.* are moot. As such, the data in Example 18 are sufficient to establish utility for the PRO1357 nucleic acids as a diagnostic tool.

In addition to the persuasive reasons articulated in Applicants' arguments of record, the PTO's reliance on Hu is also misplaced because Applicants are not relying on microarray data as discussed in Hu:

> In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study. *Hu* at 405, left column, first paragraph (emphasis added).

Instead, Applicants are relying on a more accurate and reliable method of assessing changes in mRNA level, namely quantitative PCR analysis. In a recent study by Kuo *et al.*, (Proteomics 5(4):894-906 (2005)), the authors used microarray analysis combined with proteomic analysis using two-dimensional gel electrophoresis to examine changes in gene expression in leukemia cell lines. The authors report that "[c]omparison of microarray and proteomic expression profiles showed poor correlation. Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction [RT-PCR], Western blotting and functional assays, on several genes and proteins, nonetheless, confirmed that there is indeed good correlation between mRNA and protein expression." Kuo *et al.* at Abstract (emphasis

added) (attached as Exhibit 1). Thus, even if accurate, Hu's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

In conclusion, Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1357 mRNA in normal stomach and lung tissue compared to stomach and lung tumor, respectively. The PTO has accepted that the data in Example 18 are sufficient to establish utility for the nucleic acids encoding the PRO1357 polypeptide as diagnostic tools, and therefore any challenge to the sufficiency of the data with respect to the utility of the nucleic acid is inappropriate. Therefore, the only issue which remains is whether the data in Example 18 regarding differential expression of the PRO1357 mRNA are reasonably correlated with differential expression of the PRO1357 polypeptide such that the claimed polypeptides have utility as diagnostic tools as well. As discussed below, even if the PTO has established a reasonable doubt regarding Applicants' assertion that they are reasonably correlated, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level lead to corresponding changes in protein level.

The PTO's Evidence is Not Relevant to Determining Whether a Change in mRNA Level for a Particular Gene lead to Corresponding Change in the Level of the Encoded Protein

Applicants turn next to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1357 polypeptide in stomach and lung tumors compared to normal stomach and normal lung, respectively, it is likely that the PRO1357 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic tools.

In response to Applicants' assertion, the PTO has cited Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71), Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30), Chen *et al.* (Mol. and Cell. Proteomics, (2002) 1:304-313) and Fessler *et al.* (J. Biol. Chem. (2002) 277:31291-31302) as support for its argument that "polypeptide levels cannot be accurately predicted from mRNA levels."

Applicants have previously discussed at length why Haynes and Gygi are not relevant to the issue of whether changes in mRNA level for a particular gene lead to changes in protein level. Applicants incorporate by reference the previous arguments, and will not repeat them here.

However, Applicants offer the following in an attempt to clarify the basis for Applicants' distinguishing Haynes and Gygi. Haynes and Gygi attempted to discover a global ratio common between all steady state mRNA levels and all steady state protein levels. Haynes' and Gygi's data showed that the steady state ratio of mRNA level:protein level varied for different genes, and hence no global ratio existed. Based on this, Haynes concluded that protein levels cannot be accurately calculated from mRNA levels.

In contrast, Applicants' assertions require no knowledge of a ratio between mRNA levels and protein levels, nor do Applicants' assertions require calculation of protein levels based on measured mRNA levels. Applicants simply assert that a change in mRNA level for a particular gene typically leads to a corresponding change in the encoded protein level. *See, e.g., First Grimaldi Declaration* at paragraph 7. Haynes and Gygi were concerned with a different question, and, therefore, none of Haynes' or Gygi's data or conclusions has any bearing on Applicants' assertions.

PTO has newly cited Chen *et al.* to support the assertion that there is no significant correlation between mRNA and protein expression.

In Chen, the authors examined the relationship between mRNA levels and protein levels in 76 lung adenocarcinomas and nine non-tumor lung samples. As an initial matter, it is important to note that a portion of Chen is not relevant to Applicants' assertion that changes in the level of mRNA lead to changes in the level of the encoded polypeptide. In one experiment similar to that of Haynes, Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across different genes. Based on these data, Chen reported that "no significant correlation between mRNA and protein expression was found ($r = -0.025$) if the average levels of mRNA or protein among all samples were applied across the 165 protein spots (98 genes)." *Chen* at Abstract. This measurement of a correlation across different genes is not relevant to Applicants' asserted utility for the same reasons discussed above with respect to the Haynes *et al.* reference.

Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins across the samples. Chen reports that 17% (28 of 165) of the protein spots, or 21.4% (21 of 98) of the genes, showed a statistically significant correlation between protein and mRNA expression. *Chen* at Abstract. It is these results that the PTO relies on for support.

However, read in its entirety, Chen provides scant evidence to counter Applicants' asserted utility because portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between changes in mRNA levels and changes in the corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value vs. protein value for three genes. In these figures, a wide range of mRNA expression levels were observed (approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' assertion that there is a correlation between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

The PTO relies on the fact that Chen also reports a lack of correlation for some mRNA/protein pairs to support his assertion that polypeptide levels cannot be accurately predicted from mRNA levels. However, as is explained below, the apparent lack of a correlation cannot be used as evidence that Applicants' assertion of a general correlation is wrong.

To determine if there is a correlation between changes in mRNA and changes in protein levels, one would have to conduct experiments where a measurable change in mRNA for a particular gene is observed, and then examine if there was a corresponding change in the level of the corresponding protein. Stated differently, if there is no substantial change in mRNA levels for a particular gene, one cannot measure a correlation between changes in mRNA and changes in the encoded protein for that gene. Therefore, one must know if the individual genes studied by Chen were differentially expressed to know if the observed lack of correlation has any relevance to Applicants' assertions of a general correlation between changes in mRNA and protein.

Applicants have provided in Example 18 disclosure of differential expression of mRNA encoding the PRO1357 polypeptide in stomach and lung tumors. Applicants have submitted that one skilled in the art would recognize that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. Thus, Applicants submit that one skilled in the art, based on Applicants' disclosure of differential expression of PRO1357 mRNA, would believe that the PRO1357 polypeptide is likely to also be differentially expressed. Applicants make no assertions regarding expected changes in protein levels when mRNA levels are unchanged, and evidence of protein levels when mRNA levels are unchanged has no relevance to Applicants' assertion. Importantly, unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue where one would expect to find substantial changes in the level of mRNA for certain genes. Instead, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level. *Chen* at 306, right column. Therefore, it is not known if there was any substantial difference in mRNA levels for the various studied genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed.

Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis. Since almost all samples tested by Chen were from the same type of tissue, one would expect most genes examined by Chen to have similar mRNA or protein levels across the samples. In the absence of substantial differential expression, no correlation would be observed. Because it is not known if there was a change in the level of the genes studied by Chen, *i.e.* whether they were differentially expressed, the lack of an observed correlation cannot be used to counter Applicants' assertion.

In sum, the only data reported by Chen shows substantial changes in the expression of mRNA, Figures 2A-C, which confirms Applicants' assertion that substantial changes in mRNA levels (e.g., 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, these data explain the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen – there is no indication the genes are differentially expressed. Thus, Chen's results do not refute Applicants' position. Instead, Chen supports

Applicants' position that a significant correlation between changes in mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater.

In further support of Applicants' position, Chen cites Celis *et al.* (FEBS Lett., 480:2-16 (2000)) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not relevant to Applicants' asserted utility, and therefore Chen's discussion of this issue offer no support for the PTO's position.

Given the fact that portions of Chen as well as the relevant references cited by Chen support Applicants' position, and the remainder of Chen cannot be relied on as contrary to the Applicants' position, the PTO has failed to establish a *prima facie* case that one of skill in the art would doubt Applicants' asserted utility based on any lack of correlation between changes in mRNA level and changes in the corresponding protein level.

PTO also has newly cited Fessler *et al.* to support the assertion that there is no significant correlation between mRNA and protein expression. Fessler is not contrary to Applicants' asserted utility, and actually supports Applicants' assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. Applicants make no assertions regarding changes in protein levels when mRNA levels are unchanged, nor does evidence of changes in protein levels when mRNA levels are unchanged have any relevance to Applicants' asserted utility.

Fessler *et al.* studied changes in neutrophil (PMN) gene transcription and protein expression following lipoplysaccharide (LPS) exposure. Fessler lists in Table VIII a comparison of the change in the level of mRNA for 13 up-regulated proteins and 5 down-regulated proteins. Of the 13 up-regulated proteins, a change in mRNA levels is reported for only 3 such proteins. For these 3, mRNA levels are increased in 2 and decreased in the third. Of the 5 down-regulated proteins, a change in mRNA is reported for 3 such proteins. In all 3, mRNA levels also are decreased. Thus, in 5 of the 6 cases for which a change in mRNA levels are reported, the change in the level of mRNA corresponds to the change in the level of the protein. This is consistent with Applicants' assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein.

Regarding the remainder of the proteins listed in Table VIII, in 6 instances, protein levels changed while mRNA levels were unchanged. This evidence has no relevance to Applicants' assertion that changes in mRNA levels lead to corresponding changes in protein levels, since Applicants are not asserting that changes in mRNA levels are the only cause of changes in protein levels. In the final 6 instances listed in Table VIII, protein levels changed while mRNA was noted as "absent." This evidence also has no relevance to Applicants' assertion that changes in mRNA levels causes corresponding changes in protein levels. By virtue of being "absent," it is not possible to tell whether mRNA levels were increased, decreased or remained unchanged in PMN upon contact with LPS. Nothing in these results by Fessler suggests that a change in the level of mRNA for a particular protein does not generally lead to a corresponding change in the level of the encoded protein. Accordingly, these results are not contrary to Applicants' assertions.

The PTO points to Fessler's statement regarding Table VIII that "a poor correlation was also found between corresponding transcripts and proteins." *Examiner's Answer* at 6. As is clear from the above discussion, this statement does not relate to a lack of correlation between a change in mRNA levels leading to a change in protein levels, because in 5 of 6 such instances, changes in mRNA and protein levels correlated well. Instead, this statement relates to observations in which protein levels changed when mRNA was either unchanged or "absent." As such, this statement is an observation that in addition to transcriptional activity, LPS also has post-transcriptional and possibly post-translational activity that affect protein levels, an observation which is not contrary to Applicants' assertions. Accordingly, Fessler's results are consistent with Applicants' assertion that a change in mRNA level of for a particular protein generally leads to a corresponding change in the level of the encoded protein, since 5 of 6 genes demonstrated such a correlation.

In conclusion, Applicants have shown that the Haynes reference is simply not relevant to the issue of whether a change in mRNA levels leads to a corresponding change in the level of the encoded protein, and Applicants have also shown that portions of Chen *et al.*, as well as the relevant references cited by Chen, actually support Applicants' assertion that changes in mRNA levels generally correlate with changes in the level of the encoded polypeptide. The remainder of Chen is not reliable enough to offer any support for the PTO's position. Finally, Applicants have

shown that Fessler's results are consistent with Applicants' assertions. Taken together, the PTO's arguments are not sufficient to satisfy the burden to "provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Applicants' Evidence Establishes that a Change in mRNA Level for a Particular Gene lead to Corresponding Change in the Level of the Encoded Protein

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, a copy of the declaration of Paul Polakis, Ph.D., excerpts from the Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) and (4th ed. 2002), excerpts from the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)), a reference by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, and a reference by Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002). The details of the teachings of these declarations and references, and how they support Applicants' asserted utility, are of record and will not be repeated here.

In addition to the supporting references previously submitted by Applicants, Applicants submit the following references to further support the assertion that changes in mRNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

In a comprehensive study by Orntoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45) (previously submitted with IDS, attached hereto as Exhibit 2), the authors examined gene amplification, mRNA expression level, and protein expression in pairs of non-invasive and invasive human bladder tumors. *Id.* at Abstract. The authors examined 40 well resolved abundant known proteins, and found that "[i]n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations. Only one gene showed disagreement between transcript alteration and protein alteration." *Id.* at 42, col. 2. The alternations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

In a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 3) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 4) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in 20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 5) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array

immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 6) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20Salpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Maruyama *et al.* (Am. J. Patho. 1999; 155(3):815-22) (abstract attached as Exhibit 7) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that pancreatic cancer cell lines frequently coexpressed all three Ids, "exhibiting good correlation between Id mRNA and protein levels." *Id.* at Abstract. In addition, the authors teach that all three Id mRNA levels were expressed at high levels in pancreatic cancer samples compared to normal or CP samples. At the protein level, Id-1 and Id-2 staining was faint in normal tissue, while Id-3 ranged from weak to strong. In contrast, in the cancer tissues "many of the cancer cells exhibited abundant Id-1, Id-2, and Id-3 immunoreactivity," and Id-1 and Id-2 protein was increased significantly in the cancer cells by comparison to the respective controls, mirroring the overexpression at the mRNA level. Thus, the authors report that in both cell lines and tissue samples, increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 8). In a previous study, the authors

investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Mizrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 9) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55 kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 10), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants'

assertion that changes in mRNA level, e.g. a decrease, lead to a corresponding change in the level of the encoded protein, e.g. a decrease.

In an article by Guo and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 11) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome(ARDS) by examining the expression of MIF mRNA and protein in lung tissue in ARDS and normal persons. *Id.* at Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lungs. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lungs." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular gene, e.g. an increase, generally leads to a corresponding change in the level of protein expression, e.g. an increase.

These studies are representative of numerous published studies which support Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit herewith an addition 70 references (abstracts attached as Exhibit 12) which support Applicants' assertion.

In addition to these supporting references, Applicants also submit herewith additional references which offer indirect support of Applicants' asserted utility. As discussed in detail above, Applicants have challenged the relevance of references such as Haynes *et al.*, Gygi *et al.*, Chen *et al.* and Fessler *et al.* which do not attempt to examine the correlation between a change in mRNA level and a change in the level of the corresponding protein level. Because the PTO continues to rely on these references, Applicants are submitting references which report results that are contrary to the PTO's cited references and offer indirect support for Applicants' asserted utility.

For example, in an article by Futcher *et al.* (Mol. Cell Biol. 1999; 19(11):7357-68) (abstract attached as Exhibit 13) the authors conducted a study of mRNA and protein expression in yeast which was nearly identical to the one conducted by Gygi *et al.* and reported in Haynes *et al.* Contrary to the results of the earlier study by Gygi, Futcher *et al.* report "a good correlation between protein abundance, mRNA abundance, and codon bias." *Id.* at Abstract.In a study which is more closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 14) studied the DEAD box gene, DDX1, in

retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Similarly, in an article by Papotti *et al.* (Virchows Arch. 2002; 440(5):461-75) (abstract attached as Exhibit 15) the authors examined the expression of three somatostatin receptors (SSTR) at the mRNA and protein level in forty-six tumors. *Id.* at Abstract. The authors report a "good correlation between RT-PCR [mRNA level] and IHC [protein level] data on SSTR types 2, 3, and 5." *Id.*

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 16) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 17) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 18) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC) B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression commensurate with the low protein expression level" and that in DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good correlation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 19) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases)." *Id.* at Abstract. "There was a good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO's arguments. Applicants submit herewith 26 additional references (abstracts attached as Exhibit 20) which also support Applicants' assertion in that the references report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

In summary, Applicants submit herewith a total of 113 references in addition to the declarations and references already of record which support Applicants' asserted utility, either directly or indirectly. These references support the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.,* abstracts attached as Exhibit 21). However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

In conclusion, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1357 mRNA is differentially expressed in stomach and lung tumors compared to normal stomach and lung tissue, respectively, the PRO1357 polypeptide will likewise be differentially expressed in stomach and lung tumors compared to normal stomach and lung tissue, respectively. This differential expression of the PRO1357 polypeptide makes the claimed polypeptides useful as diagnostic tools for cancer, particularly stomach and lung cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed polypeptides related to PRO1357. Applicants respectfully disagree.

Specific utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1357 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene for the PRO1357 polypeptide is expressed at least two-fold higher in normal stomach and lung tissue compared to stomach and lung tumors, respectively. These data are strong evidence that the PRO1357 gene and polypeptide are associated with stomach and lung tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1357 gene and polypeptide with a specific disease. The asserted utility for the claimed polypeptides as diagnostic tools for cancer, particularly stomach and lung tumors, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Utility – Conclusion

Applicants remind the PTO that the evidence supporting utility does not need to be direct evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa*, 93 F.3d at 1565 ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross*, 753 F.2d at 1050 (same); *Nelson*, 626 F.2d at 857 (same). In addition, utility need only be shown to be "more likely than not true." *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also maintains its rejection of pending Claims 6-8 and 11-17 under 35 U.S.C. §112, first paragraph, arguing that because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention. *See Final Office Action* at 3. For the reasons provided above, Applicants submit that Applicants have established at least one specific, substantial, and credible utility, and the PTO's rejection of Claims 6-8 and 11-17 under 35 U.S.C. § 112, first paragraph, as lacking utility should be reversed.

In addition, the PTO states that the claims lack enablement because one skilled in the art would not know how to use the claimed polypeptides. *See Final Office Action* at 3. The PTO further provides a "Wands factors" analysis based on arguments already used in asserting that the claims lack utility: the protein did not have an art-recognized use, there is evidence that nucleic acid expression does not correlate with protein expression, and the specification does not provide sufficient experimental details. The arguments directed toward lack of enablement are interspersed with and based on the same reasoning as the arguments directed toward lack of utility. *See Id.* at 4-5. Thus, the PTO demonstrates that the enablement rejection is based on lack of utility grounds. If the enablement rejection were to be based on grounds other than lack of utility, the rejections should have been imposed separately according to the M.P.E.P., which admonishes:

> To avoid confusion during examination, any rejection under 35 U.S.C. 112, first paragraph, based on grounds other than "lack of utility" should be imposed separately from any rejection imposed due to "lack of utility" under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph. *M.P.E.P.* § 2107.01 IV.

The PTO did not separate the enablement rejection from the utility rejection. More importantly, the PTO's "Wands factors" analysis is not based on any argument or evidence not similarly asserted by the Examiner in holding that the claims lack utility. While Applicants acknowledge that claims can be rejected as drawn to subject matter having utility while nevertheless lacking enablement, in the instant case, the PTO provides no reasoning and submits no evidence to support holding that the claims lack enablement that differs from the reasoning and evidence provided for holding that the claims lack utility. Thus, by repeating the same arguments and relying on the same evidence for both the utility and enablement rejections, the

PTO demonstrates that the enablement rejection is grounded on a "lack of utility" basis. As such, the Examiner's "Wands factors" analysis is grounded on a "lack of utility" basis; accordingly, the Examiner's enablement rejection is only proper if the utility rejection is proper. Applicants have argued above that one skilled in the art would have believed the claimed polypeptides have a substantial, specific and credible utility, and, thus, a utility rejection for the claimed polypeptides is not proper. Appellants further submit that because a utility rejection for the claimed polypeptides is not proper, the Examiner's enablement rejection of the claimed polypeptides also is not proper.

Even if the PTO's enablement rejection extended beyond the utility rejection, which it does not, Appellants submit that the specification enables one skilled in the art to make and use the full scope of the claims without undue experimentation. The claimed subject matter relates to polypeptides of SEQ ID NO: 78 and the polypeptide encoded by ATCC deposit 203240, and polypeptides which are at least 95% identical to those polypeptides and which can be used to make antibodies that specifically detect the polypeptide of SEQ ID NO: 78 in stomach or lung tissue. The specification discloses how to make the claimed polypeptides, for example in paragraphs [0283]-[0315] and Examples 6-9. In addition, methods for making polypeptides which are at least 95% identical to SEQ ID NO: 78 by making substitutions or deletions are also disclosed in the specification and were well known in the art. *See e.g., Specification* at ¶¶[0256]-[0271]. Methods for making and testing antibodies for specificity were well known in the art, and are disclosed in the specification, including paragraphs [0365]-[0374] and Example 10 of the specification, which specifically describes the preparation of antibodies that bind PRO polypeptides. In addition, the specification discloses that antibodies to claimed polypeptides can be used in diagnostic assays to detect the expression of PRO1357 in specific types of tissue. *See e.g., Specification* at ¶[0407]. In light of the differential expression of the nucleic acid encoding the PRO1357 polypeptide in lung and stomach tumors compared to normal lung and stomach, respectively, one of skill in the art would have expected the PRO1357 polypeptide to be differentially expressed in these tumors as well. Therefore, given the teaching in the specification on how to make and use the claimed polypeptides to detect expression of PRO1357 in specific tissues, one of skill in the art would have been enabled to practice the claimed invention without undue experimentation.

Because Appellants' specification teaches how to make and use the claimed subject matter, it must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein which are relied on for enabling support. *See M.P.E.P.* § 2164.04. It is incumbent for the PTO "to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Id.* (quoting *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). This can be done "by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact." *Id.*

The PTO refers only once to evidence, stating that "there is evidence in the prior art that even for those nucleic acids differentially expressed in tumors, a correlated expression for the encoded protein is not a given." *Final Office Action* at 4. Applicants have submitted in regard to the above utility rejection that the PTO's position is inconsistent with the knowledge in the art as a whole. Accordingly, the PTO has cited no evidence that supports the enablement rejection. As such, the PTO has not provided a reason to doubt the objective truth of the statements contained in the specification which are relied on for enabling support.

In conclusion, in the PTO's entire analysis of the Wands factors, the PTO points only once to evidence. Applicants have submitted overwhelming evidence demonstrating that the PTO's evidence is inconsistent with the knowledge in the art as a whole. Moreover, the PTO has not submitted any evidence demonstrating that one skilled in the art could not use the teachings of the specification to use the claimed polypeptides in making and testing antibodies and using antibodies to the claimed polypeptides in diagnostic assays to detect the expression of PRO1357 in specific types of tissue.

The PTO merely provides unsubstantiated arguments that the specification is insufficient because various experimental specifics were not provided in the specification, and without disclosing such specifics, it would require undue experimentation to use the claimed polypeptides. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.P.E.P.* § 2164.01; *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428

(Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (CCPA 1976). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404, citing *In re Jackson*, 217 U.S.P.Q. 804, 807-808 (Bd. App. 1982). Based on the teachings of the specification and the level of skill in the art, it was routine to make and use polypeptides such as the claimed polypeptides, in, for example, generating antibodies with the desired binding properties. No undue experimentation was required for a Ph.D. scientist with several years of experience to use these routine methods, in view of the teachings in the specification, in order to determine details such as the binding properties of the generated antibodies, the ability of an antibody to bind to a sample, or specific details of sample binding. Accordingly, it would not have required undue experimentation for one skilled in the art to make and use the claimed polypeptides. The claimed invention is, therefore, fully enabled. Moreover, the PTO provides no evidence to support an assertion that, absent various specific experimental details, it would require undue experimentation to use the claimed polypeptides. Absent such evidence, there is no reasonable basis to question the sufficiency of the disclosure.

In view of the above, Appellants submit that the specification, in view of the knowledge in the art, fully enabled the use of the claimed polypeptides. The PTO has provided no significant evidence or argument to the contrary. In view of the above, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. §102(b)

Claims 6-8 and 11-17 are rejected as anticipated under 35 U.S.C. § 102(b) over WO 01/16318 (published March 8, 2001) or WO 00/12708 (published March 9, 2000).

The PTO asserts that "[b]ecause the claims do not meet the requirements of 35 U.S.C. § 112, first paragraph, ... and the earlier application[s] likewise do not meet those requirements,

the instant application does not receive the benefit of priority to earlier filed applications." *Office Action* dated June 14, 2005, at page 12.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant "application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to U.S. Provisional Application 60/099741 filed 9/10/1998."

The sequences of SEQ ID NOs: 77 and 78 were first disclosed in U.S. Provisional Application 60/099,741 filed 9/10/1998 in Figures 1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polypeptides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Applicants submit that, in view of the arguments above, the claimed polypeptides have utility and are fully supported by the specification in accordance with 35 U.S.C. § 112, first paragraph. Moreover, Applicants submit that the previously filed applications, to which Applicants have properly claimed priority, also support the claimed polypeptides. Even if it were to be determined that Appellants are not entitled to their earliest priority date, the subject matter of the present application was disclosed in, and therefore is entitled to the priority date of, PCT Application PCT/US00/23328 filed August 24, 2000. Accordingly Applicants are entitled to a priority date no later than August 24, 2000.

WO 01/16318 was published March 8, 2001. Thus, WO 01/16318 was not published more than one year prior to Applicants' priority date, as required under 35 U.S.C. § 102(b). Accordingly, WO 01/16318 cannot be prior art under 35 U.S.C. § 102(b).

Similarly, WO 00/12708 was published March 9, 2000. Thus, WO 00/12708 was not published more than one year prior to Applicants' priority date, as required under 35 U.S.C. § 102(b). Accordingly, WO 00/12708 cannot be prior art under 35 U.S.C. § 102(b).

In view of the above, Applicants respectfully request removal of this ground of rejection of the claims.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: April 6, 2004

By: AnneMarie Kaiser
AnneMarie Kaiser
Registration No. 37,649
Attorney of Record
Customer No. 30,313
(619) 235-8550

2470033\032306